IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application: Horrobin et al.

Serial No.: 09/615,736 Group Art Unit: 1623

Filed: July 13, 2000 Examiner: Peselev, E.

For: PHARMACEUTICAL AND NUTRITIONAL COMPOSITIONS

DECLARATION UNDER 37 C.F.R. 1.132

1. I, David Horrobin, am a citizen of Great Britain and I reside in Stirling, Scotland, United Kingdom.

2. I am one of the co-inventors in the above-referenced U.S. patent application Serial No. 09/615,736.

3. I am an expert in the biochemistry of psychiatric and neurological disorders and in the biochemistry of nutrition and have researched schizophrenia and related disorders for over twenty-five years. My degrees are MA, DPHIL, BM, BCH (Oxford University, UK, equivalent to US MD PhD). I am a member of numerous professional societies in the fields of psychiatry and of nutrition.

4. I am familiar with the above-referenced U.S. patent application Serial No. 09/615,736, the Office action mailed November 23, 2001, and the references cited by the Examiner. In particular, I am familiar with the teachings of EP 0305097 (EP '097), EP 0198804 (EP '804), and WO 99/03482 (WO '482).

5. I have carefully examined the disclosures of the cited references. The references primarily provide formulations for nutritional purposes which include, depending on the given disclosure, all or most of the known nutrients which are essential. Essential fatty acids (EFAs), folic acid, vitamin B12 and pyridoxine are included in the formulations not because there is any specific virtue in combining these particular ingredients. They are included merely because they all happen to be essential nutrients and so must be included in any formulation which purports to have a general nutritional function in any field of human nutrition or medicine. However, careful inspection of these references reveals that there is nothing which draws particular attention to the unexpected synergism and therapeutic interactions which I and my co-inventor have noted between the EFAs on the one hand and the homocysteine-lowering agents on the other. In order to draw a clear and explicit distinction between the cited prior material and the new invention, we have now excluded from the claimed formulations agents that will materially change the formulations by use of the transitional phrase "consisting essentially of".

6. The combination of at least one EFA and at least one homocysteine-lowering agent in the absence of significant amounts of other micro-nutrients provides unexpected synergistic results. As evidence of the unexpected synergistic results, I have attached herewith two journal articles that provide conclusive evidence.

a. The first article by Deutch *et al.* is entitled "Menstrual Discomf rt in Danish Women Reduced by Dietary Supplements of Omega-3 PUFA and B_{12} (Fish Oil or Seal Oil Capsules)". S e Deutch *et al.* (2000) Nutrition Research 20(5):621-631 (Deutch I) Deutch I discloses the results of a study on the effect of fish oil alone or fish oil plus vitamin B_{12} in relieving menstrual discomfort. Fish oil contains the essential fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Table 4 on page 626 shows that while the number of symptoms and the pain were reduced by fish oil alone, neither reduction achieved statistical significance. In contrast, when B_{12} was added to the fish oil, both the reduction in number of symptoms ($p=0.0024$) and the reduction in pain ($p=0.015$) became clearly significant. Figure 2 also shows the enhanced symptom control achieved by administering EPA and DHA with vitamin B_{12} as compared to EPA and DHA alone. Thus, Deutch I evidences that EPA and DHA (which are both EFAs) when combined with vitamin B12 (a homocysteine-lowering agent) together provide a synergistic biological response that is greater than response of each alone and the sum thereof.

b. The second article by Deutch *et al.* is entitled "N-3 PUFA from Fish- or Seal Oil Reduce Atherogenic Risk Indications in Danish Women". See Deutch *et al.* (2000) Nutrition Research 20(8):1065-1077 (Deutch II). An elevated blood triglyceride level is a well-known and well-established risk factor with regard to the development of many types of cardiovascular disease. Deutch II shows that the combination of EPA and DHA (which are EFAs found in fish oil) when combined with vitamin B12 (a homocysteine lowering agent) lower triglyceride levels in a synergistic manner. Specifically, Table 6 shows that fish oil alone lowered triglyceride levels from 1.07 to 0.97 mmol/l after 13 weeks, which is a non-significant change. In contrast, the combination of fish oil and vitamin B_{12} lowered triglyceride levels from 1.09 to 0.79 mmol/l, which is a highly significant change ($p<0.001$). Thus, Deutch II evidences that the combination of EPA and DHA when co-administered with the homocysteine-lowering agent, vitamin B12, provide synergistic results in reducing the risk of cardiovascular disease.

7. Contrary to the Examiner's assertion in the Office Action mailed November 23, 2001, EFAs are shown to be effective in methods for treating and preventing the plurality of diseases encompassed in the claims of U.S. patent application Serial No. 09/615,736. Basically, these method claims are based on the fact that homocysteine will destroy any EFA by promoting its oxidation. Thus homocysteine will impair the therapeutic response to the administration of any EFA or combination of EFAs. Conversely, as Deutch I and II demonstrate, co-administering a homocysteine-lowering agent together with the EFAs will enhance the therapeutic response to the EFAs. Thus, the various diseases and disorders in which EFAs have been shown to be effective may be treated by the methods as claimed. There are numerous granted United States patents, many of which I am an inventor, and numerous publications, which cover most of the diseases recited in the claims. The following list provides some specific examples of the therapeutic usefulness of EFAs in the disorders recited in the claims dependent on claim 16:

a. Cardiovascular diseases. The ethyl ester of EPA is an officially approved

prescripti n pharmaceutical in Japan for the treatment of peripheral vascular disease and triglyceride low ring. The valu of EFAs in reducing the risk of cardiovascular disease is shown by Deutch II. GLA, DGLA, AA, EPA and DHA are well known for their desirable actions in reducing the risk of cardiovascular and cerebrovascular diseases by various mechanisms such as cholesterol and triglyceride lowering and anti-thrombotic and anti-arrhythmic effects. For example, these are reviewed in Horrobin DF. Abnormal membrane concentrations of 20 and 22-carbon essential fatty acids: a common link between risk factors and coronary and peripheral vascular disease. Prostaglandins Leukotrienes and Essential Fatty Acids. 1995. 53:385-96.

b. Diabetes. GLA, alone or in combination with other EFAs, is a well known agent for the treatment of diabetic complications (U.S. Patent No. 4,826,877).

c. Psychiatric diseases and disorders. EPA is effective in the treatment of depression and schizophrenia and other psychiatric and neurological disorders (e.g. U.S. Patent Nos. 4,977,187, 5,198,468, 5,120,760 and 6,331,568 and U.S. Application No. 09/492,741) while DHA alone or in combination with other EFAs is effective in the treatment of dyslexia and dyspraxia (U.S. Patent No. 6,184,251).

d. Neurological diseases and disorders. EPA and GLA and other EFAs are effective in the treatment of Huntington's disease, memory loss, tardive dyskinesia, dyspraxia dementia and other neurological disorders (e.g. the U.S. patents cited under c above, together with U.S. Patent No. 5,837,731).

e. Kidney disease. GLA and other EFAs are effective in the treatment of diabetic kidney disease (e.g. U.S. Patent No. 4,826,877). EPA and DHA are effective in the treatment of IgA nephropathy. See Donadio Jr. *et al.* A Randomized Trial of High-Dose Compared with Low-Dose Omega-3 Fatty Acids in Severe IgA Nephropathy. J. Am. Soc. Nephrol. 2001. 12:791-799; see also Schmitz *et al.* Prophylaxis of Hemodialysis Graft Thrombosis with Fish Oil. J. Am. Soc. Nephrology. 2002. 13:184-190; Serra *et al.*

f. Inflammatory and immunological disorders. These disorders are known to share many common mechanisms whether they involve smooth muscle, the gastrointestinal tract, the lungs or the joints. Deutch I shows that the invention is effective in relieving menstrual pain which is a well-known inflammatory reaction commonly relieved by the use of standard anti-inflammatory drugs such as aspirin, indomethacin or ibuprofen. Other examples from a very large literature dealing with the benefits of GLA, EPA and other EFAs in controlling inflammatory and immunological disorders are as follows: Calder *et al.* Polyunsaturated Fatty Acids and Rheumatoid Arthritis. Curr. Op. Clin. Nutr. Metabolic Care. 2001. 4:115-121.

g. Eye diseases and hearing disorders. DHA and other EFAs are effective in the treatment of macular degeneration and retinitis pigmentosa as shown by the following publications: Cho *et al.* Prospective Study of Dietary Fat and the Risk of Age-Related macular degeneration. Am. J. Clin. Nutr. 2001. 73:209-18; Birch *et al.* A Randomized C ntr lled Trial of Long-Chain Polyunsaturated Fatty Acid

Supplementation of Formula in Term Infants After Weaning at 6 wk of Age. Am J. Clin. Nutr, 2002. 75:570-80; Bazan. The Metabolism of Omega-3 Polyunsaturated Fatty Acids in the Eye. Ocular Effects f Prostaglandins and Other Eicosanoids. 1989. 95-112.

h. Obesity. Efficacy of treating obesity is evidenced by Mori *et al.* Dietary Fish as a Major Component of a Weight-loss Diet. Am. J. Clin. Nutr. 1999. 70:817-25.

i. Cancer. EPA is effective in the treatment of cancer cachexia (e.g. U.S. Patent No. 5,457,130) while many publications in the peer-reviewed literature demonstrate that GLA, DGLA, EPA and other EFAs are effective in killing cancer cells selectively (e.g. Begin ME, Ells G, Horrobin DF. Polyunsaturated fatty acid-induced cytotoxicity against tumour cells and its relationship to lipid peroxidation. J. Nat'l Cancer Instit. 1988. 80:188-194)

8. No undue experimentation is required for treating other diseases and disorders not listed in #7 above according to the present invention as claimed. It is sufficient to know that a particular condition may respond to one or other EFA, since then the response will be enhanced by combining that EFA with one or more homocysteine-lowering agents. One need only conduct routine screening and testing by methods known in the art to anyone involved in the treatment of patients.

9. Thus, in my opinion, the unexpected and superior results and responses which are described in the patent specification can be obtained by applying the information provided in that specification.

D.F.Horrobin

10. I hereby confirm that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

EXECUTED at Stirling, UK this 22 day of May 2002,

by D.F.Horrobin

David F. Horrobin, MA, DPhil, BM, BCh